

SEQUENCE LISTING

<110> Wyeth
WOLFMAN, Neil
TOMKINSON, Kathy

<120> METALLOPROTEASE ACTIVATION OF MYOSTATIN, AND METHODS OF MODULATING
MYOSTATIN ACTIVITY

<130> 08702.0128-00000

<150> US 60/486,863

<151> 2003-07-10

<150> US 60/439,164

<151> 2003-01-09

<150> US 60/411,133

<151> 2002-09-16

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<170> PatentIn version 3.1

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Leu Pro Lys Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr Asp Val	
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Gln Arg Asp Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr His	
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Leu Pro Lys Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr Asp Val
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Gln Arg Asp Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr His
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Ala Thr Thr Glu Thr Ile Ile Thr Met Pro Thr Glu Ser Asp Phe Leu
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Ile Lys Pro Met Lys Asp Gly Thr Arg Tyr Thr Gly Ile Arg Ser Leu
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Lys Leu Asp Met Asn Pro Gly Thr Gly Ile Trp Gln Ser Ile Asp Val
195 200 205

Lys Thr Val Leu Gln Asn Trp Leu Lys Gln Pro Glu Ser Asn Leu Gly
210 215 220

Ile Glu Ile Lys Ala Leu Asp Glu Asn Gly His Asp Leu Ala Val Thr
225 230 235 240

Phe Pro Gly Pro Gly Glu Asp Gly Leu Asn Pro Phe Leu Glu Val Lys
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Val Thr Asp Thr Pro Lys Arg Ser Arg Arg Asp Phe Gly Leu Asp Cys
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Asp Glu His Ser Thr Glu Ser Arg Cys Cys Arg Tyr Pro Leu Thr Val
275 280 285

Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg Tyr
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Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu Phe Val Phe Leu Gln Lys
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aca	tcg	tca	aga	cta	gaa	gcc	ata	aaa	atc	caa	atc	ctc	agt	aaa	ctt	192
Thr	Ser	Ser	Arg	Leu	Glu	Ala	Ile	Lys	Ile	Gln	Ile	Leu	Ser	Lys	Leu	
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Gln	Arg	Asp	Ala	Ser	Ser	Asp	Gly	Ser	Leu	Glu	Asp	Asp	Asp	Tyr	His	
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Ala	Arg	Thr	Glu	Thr	Val	Ile	Thr	Met	Pro	Thr	Glu	Ser	Asp	Leu	Leu	
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Thr	Gln	Val	Glu	Gly	Lys	Pro	Lys	Cys	Cys	Phe	Phe	Lys	Phe	Ser	Ser	
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245 250 255

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275 280 285

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65 70 75 80

Leu Pro Lys Ala Pro Pro Leu Leu Glu Leu Ile Asp Gln Phe Asp Val
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Gln Arg Asp Ala Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr His
100 105 110

Ala Arg Thr Glu Thr Val Ile Thr Met Pro Thr Glu Ser Asp Leu Leu

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Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg Tyr		
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Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu Phe Val Phe Leu Gln Lys		
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210	215	220	
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Leu Pro Lys Ala Pro Pro Leu Gln Glu Leu Ile Asp Gln Tyr Asp Val
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245 250 255

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260 265 270

Asp Glu His Ser Thr Glu Ser Arg Cys Cys Arg Tyr Pro Leu Thr Val
275 280 285

Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg Tyr
290 295 300

Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu Phe Val Phe Leu Gln Lys
305 310 315 320

Tyr Pro His Thr His Leu Val His Gln Ala Asn Pro Arg Gly Ser Ala
325 330 335

Gly Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met Leu Tyr
340 345 350

Phe Asn Gly Lys Glu Gln Ile Ile Tyr Gly Lys Ile Pro Ala Met Val
355 360 365

Val Asp Arg Cys Gly Cys Ser
370 375

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<211> 1125
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<220>
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<400> 7
atg cat ttt aca cag gtt tta att tct cta agt gta tta att gca tgt 48
Met His Phe Thr Gln Val Leu Ile Ser Leu Ser Val Leu Ile Ala Cys
1 5 10 15

ggt cca gtg ggt tat gga gat ata acg gcg cac cag cag cct tcc aca 96
Gly Pro Val Gly Tyr Gly Asp Ile Thr Ala His Gln Gln Pro Ser Thr
20 25 30

gcc acg gag gaa agc gag ctg tgt tcc aca tgt gag ttc aga caa cac 144
Ala Thr Glu Glu Ser Glu Leu Cys Ser Thr Cys Glu Phe Arg Gln His
35 40 45

agc aag ctg atg aga ctg cat gcc atc aag tcc caa att ctt agc aaa 192
Ser Lys Leu Met Arg Leu His Ala Ile Lys Ser Gln Ile Leu Ser Lys
50 55 60

ctc cga ctc aag cag gct cca aac atc agc cgg gac gtg gtc aag cag 240
Leu Arg Leu Lys Gln Ala Pro Asn Ile Ser Arg Asp Val Val Lys Gln

65	70	75	80	
ctg tta ccc aaa gca ccg cct ttg caa caa ctt ctg gat cag tac gat				288
Leu Leu Pro Lys Ala Pro Pro Leu Gln Gln Leu Leu Asp Gln Tyr Asp				
	85	90	95	
ggt tta gga gat gac agt aag gat gga gct gtg gaa gag gac gat gaa				336
Val Leu Gly Asp Asp Ser Lys Asp Gly Ala Val Glu Glu Asp Asp Glu				
	100	105	110	
cat gcc acc aca gag acc atc atg acc atg gcc aca gaa cct gac ccc				384
His Ala Thr Thr Glu Thr Ile Met Thr Met Ala Thr Glu Pro Asp Pro				
	115	120	125	
att gtt caa gta gat cgg aaa ccg aag tgt tgc ttt ttc tcc ttc agt				432
Ile Val Gln Val Asp Arg Lys Pro Lys Cys Cys Phe Phe Ser Phe Ser				
	130	135	140	
ccg aag atc caa gcg aac ccg atc gta aga gcg cag ctc tgg gtt cat				480
Pro Lys Ile Gln Ala Asn Arg Ile Val Arg Ala Gln Leu Trp Val His				
	145	150	155	160
ctg aga ccg gcg gag gag gcg acc acc gtc ttc tta cag ata tct cgg				528
Leu Arg Pro Ala Glu Glu Ala Thr Thr Val Phe Leu Gln Ile Ser Arg				
	165	170	175	
ctg atg ccc gtt aag gac gga gga aga cac cga ata cga tcc ctg aaa				576
Leu Met Pro Val Lys Asp Gly Gly Arg His Arg Ile Arg Ser Leu Lys				
	180	185	190	
atc gac gtg aac gca gga gtc acg tct tgg cag agt ata gac gta aag				624
Ile Asp Val Asn Ala Gly Val Thr Ser Trp Gln Ser Ile Asp Val Lys				
	195	200	205	
cag gtg ctc acg gtg tgg tta aaa caa ccg gag acc aac cga ggc atc				672
Gln Val Leu Thr Val Trp Leu Lys Gln Pro Glu Thr Asn Arg Gly Ile				
	210	215	220	
gag att aac gca tat gac gcg aag gga aac gac ttg gcc gtc act tca				720
Glu Ile Asn Ala Tyr Asp Ala Lys Gly Asn Asp Leu Ala Val Thr Ser				
	225	230	235	240
acc gag act ggg gag gat gga ctg ctc ccc ttt atg gag gtg aaa ata				768
Thr Glu Thr Gly Glu Asp Gly Leu Leu Pro Phe Met Glu Val Lys Ile				
	245	250	255	

tca gag ggc cca aaa cga atc cgg agg gac tcc gga ctg gac tgc gat 816
 Ser Glu Gly Pro Lys Arg Ile Arg Arg Asp Ser Gly Leu Asp Cys Asp
 260 265 270

gag aat tcc tca gag tct cgc tgc tgc agg tac cct ctc act gtg gac 864
 Glu Asn Ser Ser Glu Ser Arg Cys Cys Arg Tyr Pro Leu Thr Val Asp
 275 280 285

ttc gag gac ttt ggc tgg gac tgg att att gct cca aaa cgc tat aag 912
 Phe Glu Asp Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg Tyr Lys
 290 295 300

gcg aat tac tgt tca gga gaa tgc gac tac atg tac ctg cag aag tat 960
 Ala Asn Tyr Cys Ser Gly Glu Cys Asp Tyr Met Tyr Leu Gln Lys Tyr
 305 310 315 320

ccc cac acc cat ctg gtg aac aag gcc agt ccg aga gga acg gct ggg 1008
 Pro His Thr His Leu Val Asn Lys Ala Ser Pro Arg Gly Thr Ala Gly
 325 330 335

ccc tgc tgc act ccc acc aag atg tct ccc atc aac atg ctt tac ttt 1056
 Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met Leu Tyr Phe
 340 345 350

aac ggc aaa gag cag atc atc tac ggc aag atc cct tcg atg gta gta 1104
 Asn Gly Lys Glu Gln Ile Ile Tyr Gly Lys Ile Pro Ser Met Val Val
 355 360 365

gac cgc tgt ggc tgc tca tga 1125
 Asp Arg Cys Gly Cys Ser
 370

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<211> 374

<212> PRT

<213> Danio rerio

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Met His Phe Thr Gln Val Leu Ile Ser Leu Ser Val Leu Ile Ala Cys
 1 5 10 15

Gly Pro Val Gly Tyr Gly Asp Ile Thr Ala His Gln Gln Pro Ser Thr

20	25	30
Ala Thr Glu Glu Ser Glu Leu Cys Ser Thr Cys Glu Phe Arg Gln His		
35	40	45
Ser Lys Leu Met Arg Leu His Ala Ile Lys Ser Gln Ile Leu Ser Lys		
50	55	60
Leu Arg Leu Lys Gln Ala Pro Asn Ile Ser Arg Asp Val Val Lys Gln		
65	70	75
Leu Leu Pro Lys Ala Pro Pro Leu Gln Gln Leu Leu Asp Gln Tyr Asp		
85	90	95
Val Leu Gly Asp Asp Ser Lys Asp Gly Ala Val Glu Glu Asp Asp Glu		
100	105	110
His Ala Thr Thr Glu Thr Ile Met Thr Met Ala Thr Glu Pro Asp Pro		
115	120	125
Ile Val Gln Val Asp Arg Lys Pro Lys Cys Cys Phe Phe Ser Phe Ser		
130	135	140
Pro Lys Ile Gln Ala Asn Arg Ile Val Arg Ala Gln Leu Trp Val His		
145	150	155
Leu Arg Pro Ala Glu Glu Ala Thr Thr Val Phe Leu Gln Ile Ser Arg		
165	170	175
Leu Met Pro Val Lys Asp Gly Gly Arg His Arg Ile Arg Ser Leu Lys		
180	185	190
Ile Asp Val Asn Ala Gly Val Thr Ser Trp Gln Ser Ile Asp Val Lys		
195	200	205
Gln Val Leu Thr Val Trp Leu Lys Gln Pro Glu Thr Asn Arg Gly Ile		
210	215	220
Glu Ile Asn Ala Tyr Asp Ala Lys Gly Asn Asp Leu Ala Val Thr Ser		
225	230	235
Thr Glu Thr Gly Glu Asp Gly Leu Leu Pro Phe Met Glu Val Lys Ile		
245	250	255

Ser Glu Gly Pro Lys Arg Ile Arg Arg Asp Ser Gly Leu Asp Cys Asp
 260 265 270

Glu Asn Ser Ser Glu Ser Arg Cys Cys Arg Tyr Pro Leu Thr Val Asp
 275 280 285

Phe Glu Asp Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg Tyr Lys
 290 295 300

Ala Asn Tyr Cys Ser Gly Glu Cys Asp Tyr Met Tyr Leu Gln Lys Tyr
 305 310 315 320

Pro His Thr His Leu Val Asn Lys Ala Ser Pro Arg Gly Thr Ala Gly
 325 330 335

Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met Leu Tyr Phe
 340 345 350

Asn Gly Lys Glu Gln Ile Ile Tyr Gly Lys Ile Pro Ser Met Val Val
 355 360 365

Asp Arg Cys Gly Cys Ser
 370

<210> 9
 <211> 50
 <212> PRT
 <213> Homo sapiens

<400> 9

Lys Asp Val Ile Arg Gln Leu Leu Pro Lys Ala Pro Pro Leu Arg Glu
 1 5 10 15

Leu Ile Asp Gln Tyr Asp Val Gln Arg Asp Asp Ser Ser Asp Gly Ser
 20 25 30

Leu Glu Asp Asp Asp Tyr His Ala Thr Thr Glu Thr Ile Ile Thr Met
 35 40 45

Pro Thr
 50

<210> 10
 <211> 50
 <212> PRT
 <213> Artificial sequence

<220>
 <223> Mutant peptide portion of human myostatin

<400> 10

Lys Asp Val Ile Arg Gln Leu Leu Pro Lys Ala Pro Pro Leu Arg Glu
 1 5 10 15

Leu Ile Asp Gln Tyr Asp Val Gln Gln Asp Asp Ser Ser Asp Gly Ser
 20 25 30

Leu Glu Asp Asp Asp Tyr His Ala Thr Thr Glu Thr Ile Ile Thr Met
 35 40 45

Pro Thr
 50

<210> 11
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 <213> Artificial sequence

<220>
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<400> 11

Lys Asp Val Ile Arg Gln Leu Leu Pro Lys Ala Pro Pro Leu Arg Glu
 1 5 10 15

Leu Ile Asp Gln Tyr Asp Val Gln Arg Ala Asp Ser Ser Asp Gly Ser
 20 25 30

Leu Glu Asp Asp Asp Tyr His Ala Thr Thr Glu Thr Ile Ile Thr Met
 35 40 45

Pro Thr
 50

<210> 12
 <211> 40
 <212> PRT
 <213> Homo sapiens

<400> 12

Gln Leu Leu Pro Lys Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr
 1 5 10 15

Asp Val Gln Arg Asp Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp
 20 25 30

Tyr His Ala Thr Thr Glu Thr Ile
 35 40

<210> 13
 <211> 40
 <212> PRT
 <213> Artificial sequence

<220>
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<400> 13

Gln Leu Leu Pro Lys Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr
 1 5 10 15

Asp Val Gln Gln Asp Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp
 20 25 30

Tyr His Ala Thr Thr Glu Thr Ile
 35 40

<210> 14
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<220>

<223> Mutant peptide portion of human myostatin

<400> 14

Gln Leu Leu Pro Lys Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr
1 5 10 15

Asp Val Gln Arg Ala Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp
20 25 30

Tyr His Ala Thr Thr Glu Thr Ile
35 40

<210> 15

<211> 30

<212> PRT

<213> Homo sapiens

<400> 15

Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr Asp Val Gln Arg Asp
1 5 10 15

Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr His Ala
20 25 30

<210> 16

<211> 30

<212> PRT

<213> Artificial sequence

<220>

<223> Mutant peptide portion of human myostatin

<400> 16

Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr Asp Val Gln Gln Asp
1 5 10 15

Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr His Ala
20 25 30

<210> 17
 <211> 30
 <212> PRT
 <213> Artificial sequence

<220>
 <223> Mutant peptide portion of human myostatin

<400> 17

Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr Asp Val Gln Arg Ala
 1 5 10 15

Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr His Ala
 20 25 30

<210> 18
 <211> 20
 <212> PRT
 <213> Homo sapiens

<400> 18

Glu Leu Ile Asp Gln Tyr Asp Val Gln Arg Asp Asp Ser Ser Asp Gly
 1 5 10 15

Ser Leu Glu Asp
 20

<210> 19
 <211> 20
 <212> PRT
 <213> Artificial sequence

<220>
 <223> Mutant peptide portion of human myostatin

<400> 19

Glu Leu Ile Asp Gln Tyr Asp Val Gln Gln Asp Asp Ser Ser Asp Gly
 1 5 10 15

Ser Leu Glu Asp

20

<210> 20
 <211> 20
 <212> PRT
 <213> Artificial sequence

<220>
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<400> 20

Glu Leu Ile Asp Gln Tyr Asp Val Gln Arg Ala Asp Ser Ser Asp Gly
 1 5 10 15

Ser Leu Glu Asp
 20

<210> 21
 <211> 10
 <212> PRT
 <213> Homo sapiens

<400> 21

Tyr Asp Val Gln Arg Asp Asp Ser Ser Asp
 1 5 10

<210> 22
 <211> 10
 <212> PRT
 <213> Artificial sequence

<220>
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<400> 22

Tyr Asp Val Gln Gln Asp Asp Ser Ser Asp
 1 5 10

<210> 23
<211> 10
<212> PRT
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<220>
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<400> 23

Tyr Asp Val Gln Arg Ala Asp Ser Ser Asp
1 5 10